## REMARKS

Claims 1, 3-8, 10-18, 20-26, and 28-64 were pending in the present application. The Examiner has indicated that claims 49-64 are allowable. Claims 1, 18, 38, and 41-44 have been amended. Claims 36, 37, 40, and 48 have been cancelled. New claims 65-69 have been added. Accordingly, claims 1, 3-8, 10-18, 20-26, and 28-35, 38, 39, 41-47, and 49-69 are now pending.

Support for the amendment to claims 1 and 18 can be found at least in previously examined claims 40 and 48. Additional support for the amendment to claim 18 can be found at least in previously examined claim 31 and in the specification at page 16, lines 26-28. Support for the amendments to claims 42 and 44 can be found at least in previously examined claims 42 and 44. Claims 38 and 41-43 have been amended to change the dependency of each claim. Support for new claim 65 can be found at least in previously examined claims 18 and 36. Support for new claims 66 to 69 can be found at least in previously examined claims 25 and 28-30. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

No additional search is required and no new issues have been raised by the amendments made herein; support for the amendments made can be found in the claims as previously pending as outlined above. Furthermore, in view of the amendments and arguments and evidence set forth herein, the number of issues for appeal have been reduced. Therefore, the claim amendments made herein are permissible under 37 C.F.R. §1.116 as reducing the number of issues for appeal, and Applicant respectfully requests that the present Amendment and Response be entered.

Allowed Claims

Applicant gratefully acknowledges the Examiner's indication that claims 49-64 are allowable.

Rejection of 1, 3-8, 10-18, 20-26, and 28-48 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 3-8, 10-18, 20-26, and 28-48 under 35 U.S.C. §112, first paragraph. The Examiner states that the specification, "fails to provide an enabling disclosure for the method of cell-based therapy because methods of xenotransplantation of neural tissue are not routinely successful and the specification does not offer adequate specific guidance to enable one skilled in the art to practice the claimed invention over the full scope to derive a therapeutic benefit in an immunocompetent diseased animal." This rejection is respectfully traversed.

As amended, independent claim 1 is directed to a composition for transplantation into a mammalian xenogeneic subject suffering from ***a spinal cord injury or a neurodegenerative disorder resulting from a degeneration of cells of the spinal cord*** comprising isolated spinal cord cells obtained from an embryonic pig of between about 24 and about 35 days of gestation. As amended, independent claim 18 directed to a method of treating a mammalian xenogeneic subject having ***a spinal cord injury*** comprising administering to the subject a composition comprising isolated spinal cord cells obtained from an embryonic pig of between about 24 and about 35 days of gestation, such that treatment of the spinal cord injury is obtained upon administration of the composition to the subject, ***wherein the spinal cord cells or the subject are treated to reduce an immune response to the cells of the subject***. New claim 65 is directed to a method of treating a mammalian xenogeneic subject having a neurodegenerative disorder resulting from degeneration of spinal cord cells comprising administering to the subject a composition comprising isolated spinal cord cells obtained from an embryonic pig of

between about 24 and about 35 days of gestation, such that treatment of the neurodegenerative disorder is obtained upon administration of the composition to the subject, ***wherein the spinal cord cells or the subject are treated to reduce an immune response to the cells of the subject.***

Applicant maintains for the following reasons and those of record that the instant specification fully enables one of ordinary skill in the art to treat a spinal cord injury or a neurodegenerative disorder resulting from a degeneration of cells of the spinal cord.

In Applicant's response mailed January 21, 2003, Applicant provided evidence that spinal cord damage, including damage resulting from neurodegenerative disorders and spinal cord injuries, can be treated using the claimed methods. Applicant submitted a Declaration (hereinafter the "first Dinsmore Declaration") which contained results obtained from ***Phase I clinical trials approved by the FDA*** which clearly demonstrated that the specification of the instant invention fully enables one of ordinary skill in the art to use the claimed compositions and methods for treatment of spinal cord damage in general, not just for treatment of ALS and spinal cord injury.

In the Office Action dated April 24, 2003, the Examiner stated that the first Dinsmore Declaration was not persuasive, "because the description of the transplantation procedure [was] incomplete and therefore it is impossible to know if the transplantations were carried out in accordance with the teachings of the specification." In Applicant's response mailed May 24, 2004, Applicant provided a copy of a protocol provided to the physicians participating in the clinical trials from which the data presented in the first Dinsmore Declaration was obtained. The Examiner asserts that "no evidence has been offered to support that the protocol described on the protocol sheet corresponds to the protocol that was used to produce the results referred to in the Declaration of Dr. Dinsmore." The Examiner also states that "[a]ttorney argument cannot substitute for actual evidence."

Applicant provides herewith a second Declaration Under 37 C.F.R. § 1.132 of Dr. Jonathan Dinsmore (hereinafter referred to as the "second Dinsmore Declaration"). The second Dinsmore Declaration contains protocols (including the protocol submitted previously in Applicant's response of May 24, 2004) which correspond to each of the subject ID numbers, *i.e.,* SRL-05, LDS-04, WDS-03, CLO-02, and CCD-01, mentioned in the results described in Appendix E of the first Dinsmore Declaration. The protocols enclosed in Appendix F of the second Dinsmore Declaration are identical and were each provided to the physicians performing xenogeneic transplantations in accordance with the claimed invention, the results of which are described in the first Dinsmore Declaration.

The second Dinsmore Declaration is being filed to clarify that the protocol submitted previously in Applicant's response of May 24, 2004 was used to produce the results presented in the first Dinsmore Declaration. In addition, the second Dinsmore Declaration is being filed to clarify that the protocols were performed in accordance with the teachings of the specification.

The protocols described in Appendix F of the second Dinsmore Declaration show that porcine spinal cord cells were administered directly to the spinal cord of the subjects in the clinical trials. The physicians were instructed to suspend the cells prior to administration, and then told to directly inject the cell suspension into the spinal cord of the subject. As shown in Appendix F of the second Dinsmore Declaration, the instructions note that the number of injections warranted for individual transplantation procedures depended on the extent of the spinal cord damage.

Furthermore, as evidence that the teachings of the instant specification provide sufficient guidance for one of ordinary skill in the art to make and use the claimed invention, in addition to the protocols enclosed as Appendix F, procedural reports from each subject are provided in Appendix G of the second Dinsmore Declaration. The

procedural reports provide a summary by each physician performing the xenotransplantation.

The Examiner states that the previously submitted protocol (which is included in Appendix F of the second Dinsmore Declaration submitted herewith) "does not disclose the actual number of cells injected, the actual number of injection sites..." Applicant respectfully submits that the details described by the Examiner regarding cell number and injection sites are taught by the specification and are also described in the protocols of Appendix F of the second Dinsmore Declaration. As shown in Appendix G of the second Dinsmore Declaration, each report includes information regarding the number of injection sites, and the location of each injection site, and the volume of cells injected into the subject. Based on the volume of cells injected, one can determine the number of cells injected as the protocols state that 20 microliters "is equal to 2 million cells." In addition, as described in Applicant's response of May 24, 2004, the specification teaches that this number of cells can be injected into a subject. Applicant teaches in the specification that the administration dosage of porcine cells can be determined by performing experiments in rats. Applicant teaches how to extrapolate the dosing of human equivalents from the rat experiments (see page 14, lines 3-13 of specification), and provides an exemplary dosage in Example 1, teaching that transplantations can be performed with an approximate concentration of cells at 100,000 cells per microliter (see page 27 of the specification). The protocols provided in Appendix F of the second Dinsmore Declaration teach that "[t]he volume of cells to be injected at each site is a maximum of 20 microliters, which is equal to 2 million cells." Thus, as described as a working example of the instant specification, the concentration of the cell suspension in the protocols of Appendix F of the second Dinsmore Declaration is 100,000 cells per microliter.

With respect to the delivery of the cells of the invention, Applicant teaches that porcine spinal cord cells are commonly introduced into a subject by "direct stereotaxic injection of the cells into the area of spinal cord damage as well as areas rostral and caudal to that area" (see page 13, line 38 to page 14, line 1 of the instant specification). In the specification Applicant also describes a working example using the hemisected rat model, where hemisection of a rat is performed on the right side of the spinal cord between thoracic region T13 and lumbar region L1 (see page 27, lines 37-38 of specification). Applicant teaches that fetal porcine cells were subsequently transplanted into the hemisected space, *i.e.,* into the area of spinal cord damage.

In accordance with the teachings of the specification, the protocols provided in Appendix F of the second Dinsmore Declaration describe identifying the area of spinal cord damage to determine the area of the spinal cord where the embryonic porcine spinal cord cells will be delivered. Applicant submits that one of ordinary skill in the art would recognize that the number of injection sites is dependent upon the nature of the spinal cord damage. In support of this assertion, Applicant refers to Appendix G of the second Dinsmore Declaration which describes procedural reports from actual transplantation procedures. As described in the procedural report for subject CCD-01, for example, six injections were performed to treat a cervical spinal cord injury in the injury location of C6 to C8.

The protocols described in Appendix F of the second Dinsmore Declaration are consistent with the teachings of the instant specification and were used to successfully treat patients having a spinal cord injury or a neurodegenerative disorder resulting from a degeneration of cells of the spinal cord, as shown in the results presented in the first Dinsmore Declaration. Accordingly, the protocols and reports described in Appendices F and G of the second Dinsmore Declaration correspond to the protocols used to produce the results submitted in the first Dinsmore Declaration which demonstrate that

transplantation of xenogeneic porcine spinal cord cells can be used effectively as treatment for improving both the sensory and motor function of human subjects having spinal cord injury or a neurodegenerative disorder.

The Examiner maintains that, "[t]he art demonstrates that methods of xenotransplantation of neural tissue is unpredictable due to the immune response of the host, which leads to graft rejection if adequate immunosuppression cannot be achieved." The Examiner describes various references previously cited in support of the above assertion, and states that neither the previously submitted Declaration nor the previously submitted protocol address the issue of immunosuppression.

The instant specification provides evidence that efforts can be taken, *e.g.*, immunosuppressive drugs and/or masking of cells, to reduce the risk of rejection of the xenotransplanted cells. For example, Applicant teaches various methods of inhibiting rejection of the transplantation from page 16 to 19 of the instant specification. Applicant teaches that inhibition of an immunological response can be achieved using a number of different means, including altering at least one immunogenic cell surface antigen, such as an MHC class I antigen, or administering an agent which inhibits T cell activity, such as the immunosuppressive drug cyclosporin A. In the working examples of the specification, Applicant also teaches that acceptance of transplanted porcine spinal cord cells in rat recipients can be improved either by treating the rats with cyclosporin or transplanting masked porcine spinal cord cells using an antibody specific for porcine MHC class I antigen. Furthermore, Applicant submits that one of ordinary skill in the art would recognize that it may be necessary to prevent rejection of transplanted embryonic porcine spinal cord cells in human subjects.

Based on the teachings in the specification and the knowledge in the art regarding graft rejection at the time of filing, one of ordinary skill in the art would have been able to make and use the claimed invention without undue experimentation. At the time the

invention was made immunosuppression during transplantation was routine in the art. Armed with the teachings of the specification and the knowledge of one of skill in the art, one of ordinary skill in the art, e.g., a physician working as part of a transplant team, would be able to reduce the risk of cell rejection by, for example, treating the cells to be transplanted ( e.g., by masking of the porcine cells) as taught in the instant specification and/or by administration of immunosuppressive drugs. The data and protocols described in the first Dinsmore Declaration and the second Dinsmore Declaration submitted herewith were performed using efforts to prevent graft rejection, as described in the attached Declaration.

In the interest of expediting prosecution, claim 18 as amended and new claim 65 recite that the spinal cord cells or the subject are treated to reduce an immune response to the cells of the subject. Claim 1 is directed to a composition. It is clear that the claimed compositions can be administered in conjunction with immunosuppression without requiring that the immunosuppressant and the cells be administered as part of the same composition. The claimed composition should not be required to recite every component necessary to enable one of ordinary skill in the art to use the invention (*Rambus Inc. v. Infineon Technologies AG* 318 F.3d 1081 (Fed. Cir. 2003). Because immunosuppression was well known in the art and would be administered as a matter of routine when found to be appropriate by the skilled artisan, Applicant contends that the composition claims should not be required to recite this limitation in order to be enabeling.

Regarding the references cited by the Examiner, Applicant maintains that the cited references do not support the Examiner's assertion that Applicant has not enabled the claimed invention because of the unpredictability of the art for the reasons of record and those described below.

Applicant notes that the Larsson, Armstrong, and Brevig references relate specifically to xenotransplantation of ***brain tissue.*** The Armstrong reference describes

transplantation of fetal neural precursor cells obtained from the cerebral cortex of fetal pigs, while the Larsson reference describes transplantation of fetal ventral mesencephalon cells. Applicant submits that these references pertaining to xenotransplantation of ***brain tissue*** do not demonstrate the asserted unpredictability of claims pertaining to xenotransplantation of ***spinal cord cells for the treatment of a spinal cord injury or a neurodegenerative disorder resulting from degeneration of cells of the spinal cord.***

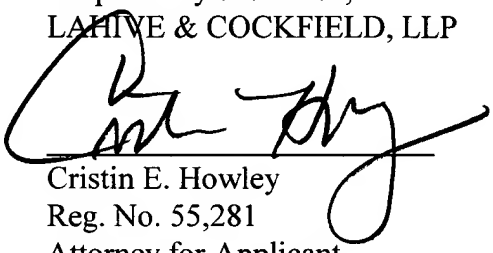
In addition, Applicant maintains that the teachings of Rowe and Dorling *et al.* do not pertain to the claimed invention, as both of these cited references relate to ***whole organ*** transplantation, in contrast to the claimed invention which specifies a composition comprising ***isolated spinal cord cells***.

In contrast to the Examiner's assertion, the working examples of the specification, the first Dinsmore Declaration, and the second Dinsmore Declaration submitted herewith demonstrate that the claimed methods and compositions of porcine spinal cord cells for use in xenotransplantation produce predictable, successful results. Furthermore, the protocols described in Appendix F of the enclosed second Dinsmore Declaration are consistent with the teachings of the instant specification and were used to successfully treat subjects having a spinal cord injury or a neurodegenerative disorder. Thus, Applicant submits that the specification fully enables one of skill in the art to perform the claimed transplantation without undue experimentation, evidenced by the working examples in the specification, the protocols which were used in actual clinical transplantations, and the results produced from said teachings presented in the first Dinsmore Declaration.

## CONCLUSION

It is respectfully submitted that this application is in condition for allowance. If the Examiner believes that a telephone conversation with Applicant's Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



Cristin E. Howley
Reg. No. 55,281
Attorney for Applicant

28 State Street
Boston, Massachusetts 02109
Telephone: (617) 227-7400
Facsimile: (617) 742-4214

Date: February 14, 2005